Table S1: Screening of the potentially active compounds in Xiaoyao San (XYS)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ID | Compound | OB (%) | DL | Herb |
| C1 | Quercetin | 46.43 | 0.28 | *Glycyrrhiza uralensish, Bupleurum chinense* |
| C2 | Isorhamnetin | 49.6 | 0.31 | *Glycyrrhiza uralensis, Bupleurum chinense* |
| C3 | Kaempferol | 41.88 | 0.24 | *Glycyrrhiza uralensis, Paeonia lactiflora, Bupleurum chinense* |
| C4 | Sitosterol | 36.91 | 0.75 | *Glycyrrhiza uralensis, Paeonia lactiflora* |
| C5 | Mairin | 55.38 | 0.78 | *Glycyrrhiza uralensis, Paeonia lactiflora* |
| C6 | Xambioona | 54.85 | 0.87 | *Glycyrrhiza uralensis* |
| C7 | Vestitol | 74.66 | 0.21 | *Glycyrrhiza uralensis* |
| C8 | Sigmoidin-B | 34.88 | 0.41 | *Glycyrrhiza uralensis* |
| C9 | shinpterocarpin | 80.3 | 0.73 | *Glycyrrhiza uralensis* |
| C10 | Semilicoisoflavone B | 48.78 | 0.55 | *Glycyrrhiza uralensis* |
| C11 | Quercetin der. | 46.45 | 0.33 | *Glycyrrhiza uralensis* |
| C12 | Phaseolinisoflavan | 32.01 | 0.45 | *Glycyrrhiza uralensis* |
| C13 | Phaseol | 78.77 | 0.58 | *Glycyrrhiza uralensis* |
| C14 | Odoratin | 49.95 | 0.3 | *Glycyrrhiza uralensis* |
| C15 | Naringenin | 59.29 | 0.21 | *Glycyrrhiza uralensis* |
| C16 | Medicarpin | 49.22 | 0.34 | *Glycyrrhiza uralensis* |
| C17 | Lupiwighteone | 51.64 | 0.37 | *Glycyrrhiza uralensis* |
| C18 | Liquiritin | 65.69 | 0.74 | *Glycyrrhiza uralensis* |
| C19 | Licoricone | 63.58 | 0.47 | *Glycyrrhiza uralensis* |
| C20 | Licorice glycoside E | 32.89 | 0.27 | *Glycyrrhiza uralensis* |
| C21 | Licopyranocoumarin | 80.36 | 0.65 | *Glycyrrhiza uralensis* |
| C22 | Licoisoflavone B | 38.93 | 0.55 | *Glycyrrhiza uralensis* |
| C23 | Licoisoflavone | 41.61 | 0.42 | *Glycyrrhiza uralensis* |
| C24 | Licoisoflavanone | 52.47 | 0.54 | *Glycyrrhiza uralensis* |
| C25 | Licocoumarone | 33.21 | 0.36 | *Glycyrrhiza uralensis* |
| C26 | Licochalcone G | 49.25 | 0.32 | *Glycyrrhiza uralensis* |
| C27 | Licochalcone B | 76.76 | 0.19 | *Glycyrrhiza uralensis* |
| C28 | Licochalcone a | 40.79 | 0.29 | *Glycyrrhiza uralensis* |
| C29 | Licoagroisoflavone | 57.28 | 0.49 | *Glycyrrhiza uralensis* |
| C30 | Licoagrocarpin | 58.81 | 0.58 | *Glycyrrhiza uralensis* |
| C31 | Kanzonols W | 50.48 | 0.52 | *Glycyrrhiza uralensis* |
| C32 | Kanzonol F | 32.47 | 0.89 | *Glycyrrhiza uralensis* |
| C33 | Jaranol | 50.83 | 0.29 | *Glycyrrhiza uralensis* |
| C34 | Isotrifoliol | 31.94 | 0.42 | *Glycyrrhiza uralensis* |
| C35 | Isolicoflavonol | 45.17 | 0.42 | *Glycyrrhiza uralensis* |
| C36 | Isoglycyrol | 44.7 | 0.84 | *Glycyrrhiza uralensis* |
| C37 | Inflacoumarin A | 39.71 | 0.33 | *Glycyrrhiza uralensis* |
| C38 | Inermine | 75.18 | 0.54 | *Glycyrrhiza uralensis* |
| C39 | Icos-5-enoic acid | 30.7 | 0.2 | *Glycyrrhiza uralensis* |
| C40 | HMO | 38.37 | 0.21 | *Glycyrrhiza uralensis* |
| C41 | Glyzaglabrin | 61.07 | 0.35 | *Glycyrrhiza uralensis* |
| C42 | Glypallichalcone | 61.6 | 0.19 | *Glycyrrhiza uralensis* |
| C43 | Glycyrrhiza flavonol A | 41.28 | 0.6 | *Glycyrrhiza uralensis* |
| C44 | Glycyroside | 37.25 | 0.79 | *Glycyrrhiza uralensis* |
| C45 | Glycyrol | 90.78 | 0.67 | *Glycyrrhiza uralensis* |
| C46 | Glycyrin | 52.61 | 0.47 | *Glycyrrhiza uralensis* |
| C47 | Glyasperins M | 72.67 | 0.59 | *Glycyrrhiza uralensis* |
| C48 | Glyasperin F | 75.84 | 0.54 | *Glycyrrhiza uralensis* |
| C49 | Glyasperin C | 45.56 | 0.4 | *Glycyrrhiza uralensis* |
| C50 | Glyasperin B | 65.22 | 0.44 | *Glycyrrhiza uralensis* |
| C51 | Glepidotin B | 64.46 | 0.34 | *Glycyrrhiza uralensis* |
| C52 | Glepidotin A | 44.72 | 0.35 | *Glycyrrhiza uralensis* |
| C53 | Glabrone | 52.51 | 0.5 | *Glycyrrhiza uralensis* |
| C54 | Glabridin | 53.25 | 0.47 | *Glycyrrhiza uralensis* |
| C55 | Glabrene | 46.27 | 0.44 | *Glycyrrhiza uralensis* |
| C56 | Glabranin | 52.9 | 0.31 | *Glycyrrhiza uralensis* |
| C57 | Gancaonin H | 50.1 | 0.78 | *Glycyrrhiza uralensis* |
| C58 | Gancaonin G | 60.44 | 0.39 | *Glycyrrhiza uralensis* |
| C59 | Gancaonin B | 48.79 | 0.45 | *Glycyrrhiza uralensis* |
| C60 | Gancaonin A | 51.08 | 0.4 | *Glycyrrhiza uralensis* |
| C61 | Gadelaidic acid | 30.7 | 0.2 | *Glycyrrhiza uralensis* |
| C62 | Formononetin | 69.67 | 0.21 | *Glycyrrhiza uralensis* |
| C63 | Eurycarpin A | 43.28 | 0.37 | *Glycyrrhiza uralensis* |
| C64 | Euchrenone | 30.29 | 0.57 | *Glycyrrhiza uralensis* |
| C65 | DFV | 32.76 | 0.18 | *Glycyrrhiza uralensis* |
| C66 | Dehydroglyasperins C | 53.82 | 0.37 | *Glycyrrhiza uralensis* |
| C67 | Calycosin | 47.75 | 0.24 | *Glycyrrhiza uralensis* |
| C68 | 8-prenylated eriodictyol | 53.79 | 0.4 | *Glycyrrhiza uralensis* |
| C69 | 8-(6-hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol | 58.44 | 0.38 | *Glycyrrhiza uralensis* |
| C70 | 7-Methoxy-2-methyl isoflavone | 42.56 | 0.2 | *Glycyrrhiza uralensis* |
| C71 | 7-Acetoxy-2-methylisoflavone | 38.92 | 0.26 | *Glycyrrhiza uralensis* |
| C72 | 7,2',4'-trihydroxy－5-methoxy-3－arylcoumarin | 83.71 | 0.27 | *Glycyrrhiza uralensis* |
| C73 | 6-prenylated eriodictyol | 39.22 | 0.41 | *Glycyrrhiza uralensis* |
| C74 | 5,7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone | 30.49 | 0.41 | *Glycyrrhiza uralensis* |
| C75 | 3'-Methoxyglabridin | 46.16 | 0.57 | *Glycyrrhiza uralensis* |
| C76 | 3'-Hydroxy-4'-O-Methylglabridin | 43.71 | 0.57 | *Glycyrrhiza uralensis* |
| C77 | 3,22-Dihydroxy-11-oxo-delta(12)-oleanene-27-alpha-methoxycarbonyl-29-oic acid | 34.32 | 0.55 | *Glycyrrhiza uralensis* |
| C78 | 3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone | 66.37 | 0.41 | *Glycyrrhiza uralensis* |
| C79 | 3-(2,4-dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin | 59.62 | 0.43 | *Glycyrrhiza uralensis* |
| C80 | 2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol | 36.21 | 0.52 | *Glycyrrhiza uralensis* |
| C81 | 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone | 44.15 | 0.41 | *Glycyrrhiza uralensis* |
| C82 | 1-Methoxyphaseollidin | 69.98 | 0.64 | *Glycyrrhiza uralensis* |
| C83 | 18α-hydroxyglycyrrhetic acid | 41.16 | 0.71 | *Glycyrrhiza uralensis* |
| C84 | 1,3-dihydroxy-9-methoxy-6-benzofurano[3,2-c]chromenone | 48.14 | 0.43 | *Glycyrrhiza uralensis* |
| C85 | 1,3-dihydroxy-8,9-dimethoxy-6-benzofurano[3,2-c]chromenone | 62.9 | 0.53 | *Glycyrrhiza uralensis* |
| C86 | (E)-3-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2,4-dihydroxyphenyl)prop-2-en-1-one | 46.27 | 0.31 | *Glycyrrhiza uralensis* |
| C87 | (E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethylchromen-6-yl)prop-2-en-1-one | 39.62 | 0.35 | *Glycyrrhiza uralensis* |
| C88 | (2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one | 36.57 | 0.32 | *Glycyrrhiza uralensis* |
| C89 | (2S)-6-(2,4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2,3-dihydrofuro[3,2-g]chromen-7-one | 60.25 | 0.63 | *Glycyrrhiza uralensis* |
| C90 | (2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]-8,8-dimethyl-2,3-dihydropyrano[2,3-f]chromen-4-one | 31.79 | 0.72 | *Glycyrrhiza uralensis* |
| C91 | (2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one | 71.12 | 0.18 | *Glycyrrhiza uralensis* |
| C92 | (−-Medicocarpin | 40.99 | 0.95 | *Glycyrrhiza uralensis* |
| C93 | Trametenolic acid | 38.71 | 0.8 | *Wolfiporia cocos* |
| C94 | Poricoic acid C | 38.15 | 0.75 | *Wolfiporia cocos* |
| C95 | Poricoic acid B | 30.52 | 0.75 | *Wolfiporia cocos* |
| C96 | Poricoic acid A | 30.61 | 0.76 | *Wolfiporia cocos* |
| C97 | Pachymic acid | 33.63 | 0.81 | *Wolfiporia cocos* |
| C98 | Hederagenin | 36.91 | 0.75 | *Wolfiporia cocos* |
| C99 | Ergosterol peroxide | 40.36 | 0.81 | *Wolfiporia cocos* |
| C100 | Ergosta-7,22E-dien-3beta-ol | 43.51 | 0.72 | *Wolfiporia cocos* |
| C101 | Dehydroeburicoic acid | 44.17 | 0.83 | *Wolfiporia cocos* |
| C102 | Cerevisterol | 37.96 | 0.77 | *Wolfiporia cocos* |
| C103 | 7,9(11)-dehydropachymic acid | 35.11 | 0.81 | *Wolfiporia cocos* |
| C104 | 3beta-Hydroxy-24-methylene-8-lanostene-21-oic acid | 38.7 | 0.81 | *Wolfiporia cocos* |
| C105 | (2R)-2-[(5R,10S,13R,14R,16R,17R)-16-hydroxy-3-keto-4,4,10,13,14-pentamethyl-1,2,5,6,12,15,16,17-octahydrocyclopenta[a]phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid | 38.26 | 0.82 | *Wolfiporia cocos* |
| C106 | (2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid | 31.07 | 0.82 | *Wolfiporia cocos* |
| C107 | Stigmasterol | 43.83 | 0.76 | *Angelica sinensis, Bupleurum chinense* |
| C108 | -sitosterol | 1 | 0.99 | *Angelica sinensis, Paeonia lactiflora* |
| C109 | α-spinasterol | 42.98 | 0.76 | *Bupleurum chinense* |
| C110 | Troxerutin | 31.6 | 0.28 | *Bupleurum chinense* |
| C111 | Sainfuran | 79.91 | 0.23 | *Bupleurum chinense* |
| C112 | Saikosaponin c\_qt | 30.5 | 0.63 | *Bupleurum chinense* |
| C113 | Petunidin | 30.05 | 0.31 | *Bupleurum chinense* |
| C114 | Octalupine | 47.82 | 0.28 | *Bupleurum chinense* |
| C115 | Longikaurin A | 47.72 | 0.53 | *Bupleurum chinense* |
| C116 | Linoleyl acetate | 42.1 | 0.2 | *Bupleurum chinense* |
| C117 | Cubebin | 57.13 | 0.64 | *Bupleurum chinense* |
| C118 | Baicalin | 40.12 | 0.75 | *Bupleurum chinense* |
| C119 | Areapillin | 48.96 | 0.41 | *Bupleurum chinense* |
| C120 | 3,5,6,7-tetramethoxy-2-(3,4,5-trimethoxyphenyl)chromone | 31.97 | 0.59 | *Bupleurum chinense* |
| C121 | (+)-Anomalin | 46.06 | 0.66 | *Bupleurum chinense* |
| C122 | α-Amyrin | 39.51 | 0.76 | *Atractylodes macrocephala* |
| C123 | 8β-ethoxy atractylenolide Ⅲ | 35.95 | 0.21 | *Atractylodes macrocephala* |
| C124 | 3β-acetoxyatractylone | 54.07 | 0.22 | *Atractylodes macrocephala* |
| C125 | 14-acetyl-12-senecioyl-2E,8Z,10E-atractylentriol | 63.37 | 0.3 | *Atractylodes macrocephala* |
| C126 | 14-acetyl-12-senecioyl-2E,8E,10E-atractylentriol | 60.31 | 0.31 | *Atractylodes macrocephala* |
| C127 | 12-senecioyl-2E,8E,10E-atractylentriol | 62.4 | 0.22 | *Atractylodes macrocephala* |
| C128 | (3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-[(2R,5S)-5-propan-2-yloctan-2-yl]-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol | 36.23 | 0.78 | *Atractylodes macrocephala* |
| C129 | Paeoniflorin | 53.87 | 0.79 | *Paeonia lactiflora* |
| C130 | Paeoniflorgenone | 87.59 | 0.37 | *Paeonia lactiflora* |
| C131 | Lactiflorin | 49.12 | 0.8 | *Paeonia lactiflora* |
| C132 | Benzoyl paeoniflorin | 31.27 | 0.75 | *Paeonia lactiflora* |
| C133 | Albiflorin\_qt | 66.64 | 0.33 | *Paeonia lactiflora* |
| C134 | 11alpha,12alpha-epoxy-3beta-23-dihydroxy-30-norolean-20-en-28,12beta-olide | 64.77 | 0.38 | *Paeonia lactiflora* |
| C135 | (3S,5R,8R,9R,10S,14S)-3,17-dihydroxy-4,4,8,10,14-pentamethyl-2,3,5,6,7,9-hexahydro-1H-cyclopenta[a]phenanthrene-15,16-dione | 43.56 | 0.53 | *Paeonia lactiflora* |
| C136 | (+)-catechin | 54.83 | 0.24 | *Paeonia lactiflora* |

Table S2: Functional enrichment of genes using the GO database

|  |  |  |  |
| --- | --- | --- | --- |
| GO category | Description | Gene identification | Count |
| BP | Metabolism | *TYR; TBXAS1; POR; PON1; NQO1; NADK; MT-CO3; MT-CO1; HSD3B1; HSD11B1; HPSE; HMGCR; HK2; GSTP1; GSTM1; GSK3B; DUOX2; CYP3A4; CYP2C19; CYP27B1; CYP1B1; CYP1A1; COX5B; COX5A; COX4I1; CES1; AMPD3; ALOX5; AKR1B1; ADH1C; ADH1B; ACP1; ACHE; ACACA; ABAT;* | 35 |
| BP | Xenobiotic metabolism | *NQO1; GSTM1; CYP2D6;* | 3 |
| BP | Energy pathways | *TYR; TBXAS1; POR; PON1; NQO1; NADK; MT-CO3; MT-CO1; HSD3B1; HPSE; HMGCR; HK2; GSTP1; GSTM1; GSK3B; DUOX2; CYP3A4; CYP2C19; CYP27B1; CYP1B1; CYP1A1; COX5B; COX5A; COX4I1; AMPD3; ALOX5; AKR1B1; ADH1C; ADH1B; ACP1; ACHE; ACACA; ABAT;* | 33 |
| BP | Signal transduction | *VEGFA; VCAM1; TBXA2R; SRC; SIGMAR1; SELP; ROCK2; ROCK1; RAF1; PTGER3; PRLR; PRKCA; PGR; OXTR; NR3C2; NR1I2; NPPB; MYLK; MTOR; MAPK8; MAPK10; LDLR; LCK; JAK3; JAK2; JAK1; ITGB2; IKBKB; IGFBP3; IGF2; ICAM1; HRH3; HRH2; HCK; GRM8; GRM5; GRM2; GRIN2C; GRIN2B; GCGR; FYN; FGFR1; ERBB2; EGFR; DRD3; DAPK1; CNR1; CHRNA3; CHRM1; CHEK2; CHEK1; CDK4; CCR5; CCND1; BRAF; AVPR2; AR; ANXA1; AKT2; ADRA1A;* | 60 |
| BP | Apoptosis | *LGALS9; IGFBP3; CASP9; CASP3; CASP1; BCL2; BAX; BID; BAD;* | 9 |
| BP | Cell communication | *VEGFA; VCAM1; TBXA2R; SIGMAR1; SELP; ROCK2; ROCK1; RAF1; PTGER3; PRLR; PRKCA; OXTR; NR3C2; NPPB; MYLK; MTOR; LDLR; LCK; JAK3; JAK2; JAK1; ITGB2; IKBKB; IGFBP3; IGF2; ICAM1; HRH3; HRH2; HCK; GRM8; GRM2; GRIN2C; GRIN2B; GCGR; FYN; FGFR1; ERBB2; EGFR; DRD3; DAPK1; CNR1; CHRNA3; CHRM1; CHEK2; CHEK1; CDK4; CCR5; CCND1; BRAF; AVPR2; AR; ANXA1; AKT2; ADRA1A;* | 54 |
| CC | Endoplasmic reticulum | *TYR; TP63; TBXAS1; SREBF2; SREBF1; SIGMAR1; PTGS1; PRKCA; POR; MTTP; MME; HTR3A; HSD3B1; HSD11B1; HPSE; HMGCR; GRIN1; GRIA2; FOS; EIF2AK3; DUOX2; CYP3A4; CYP2D6; CYP2C19; CYP1B1; CYP1A1; CTSD; CFTR; CAV1; BCL2; BACE1; BAX; AVPR2; ATP1A3; APOB; APEX1; AHSA1;* | 37 |
| CC | Plasma membrane | *VCAM1; TRPM8; TBXA2R; SRC; SLC2A4; SIGMAR1; SELP; SELE; RAF1; PTGS1; PTGER3; PRLR; PRKCA; POR; PON1; PLAU; OXTR; OLR1; NR3C1; NQO1; MYLK; MTOR; MME; LGALS9; LDLR; LCK; ITGB2; IKBKB; IGFBP3; IDE; ICAM1; HTR3A; HSPB1; HRH3; HRH2; HCK; GRM8; GRM5; GRM2; GRIN2C; GRIN2B; GRIN1; GRIA2; GCGR; GC; FYN; FGFR1; F7; F11; ESR1; ERBB2; EGFR; ECE1; DUOX2; DRD3; DAPK1; CNR1; CHRNA3; CHRM2; CFTR; CCR5; CAV1; CASP3; BRAF; BACE1; AVPR2; ATP1A3; AR; APOB; ANXA1; AKT2; ADAM17; ACHE; ACE; ABCC1;* | 75 |
| CC | Cytoplasm | *VEGFA; VDR; TYR; TTR; TP63; TNKS; TDP1; SREBF2; SRC; RUVBL2; ROCK2; ROCK1; RELA; RAF1; PTGS1; PRKCA; PPARG; PPARA; POLB; PLAU; PGR; PARP1; NR3C1; NR1I2; NQO1; NFKBIA; NFKB1; NFE2L2; NADK; MYLK; MTTP; MTOR; MME; MAPK8; MAPK10; LGALS9; LCK; JAK3; JAK2; JAK1; IRF1; IKBKB; IGFBP3; IDE; ICAM1; HSPB1; HSPA8; HSP90AA1; HSF1; HSD3B1; HPSE; HIF1A; HDAC6; HCK; GSTP1; GSTM1; GSK3B; GC; FYN; FGFR1; FABP1; ESRRG; ESR2; ESR1; ERBB2; ELK1; EGFR; ECE1; DUOX2; DAPK1; CYP3A4; CYP27B1; CYP1B1; CTSD; COX5B; COX4I1; CHEK2; CDK4; CDK2; CCR5; CCND1; CASP9; CASP3; CASP1; BRAF; BCL2; BAX; BID; BAD; AR; APEX1; ANXA1; AMPD3; ALOX5; ALB; AKT2; AKR1B1; AHSA1; AHR; ADH1C; ACP1; ACACA; ABCC1;* | 103 |
| CC | Extracellular space | *VEGFA; VCAM1; SELP; SELE; REN; PON1; PLAU; NPPB; IL6; IGFBP3; IDE; ICAM1; HSP90AA1; F11; EGFR; CTSD; COL3A1; ALB; AKR1B1; ACE;* | 20 |
| CC | External side of plasma membrane | *VCAM1; SLC2A4; SELP; LDLR; ECE1; CCR5; ACE;* | 7 |
| CC | Integral to plasma membrane | *TBXA2R; SLC2A4; SIGMAR1; SELP; PTGER3; OXTR; OLR1; MME; LDLR; ICAM1; HTR3A; HRH3; HRH2; GRM8; GRM5; GRM2; GRIN2C; GRIN2B; GRIN1; FGFR1; DRD3; CNR1; CHRM2; CHRM1; CCR5; BACE1; AVPR2; ADRA1A; ADAM17; ABCC1;* | 30 |
| CC | Mitochondrial outer membrane | *RAF1; HK2; BCL2; BAX; BID; BAD;* | 6 |
| CC | Caveola | *SRC; SELE; HDAC6; HCK; CAV1;* | 5 |
| CC | Endoplasmic reticulum membrane | *SREBF1; HSD3B1; HSD11B1; HMGCR; GRM5; EIF2AK3; CYP3A4; CYP2C19; CYP1B1; BAX;* | 10 |
| CC | Microsome | *TNKS; SREBF1; NQO1; HSD3B1; HMGCR; CYP3A4; CYP2D6; CYP2C19; CYP1A1; APOB;* | 10 |
| CC | Cytosol | *SRC; ROCK2; ROCK1; RELA; RAF1; PRKCA; NFKBIA; NFKB1; NADK; MYLK; MTOR; MAPK8; LCK; JAK1; IKBKB; HSPA8; HSP90AA1; GSK3B; FYN; CDK4; CDK2; CCND1; CASP9; CASP3; BCL2; BAX; BID; BAD; ALOX5; AKT2; AKR1B1;* | 31 |
| CC | Nuclear membrane | *TNKS; SREBF1; SIGMAR1; PTGER3; GRM5; BCL2; ALOX5;* | 7 |
| CC | Cyclin-dependent protein kinase holoenzyme complex | *CDK4; CDK2; CCND1;* | 3 |
| CC | Endosome | *TNKS; SELE; MME; LDLR; IDE; GC; FYN; EGFR; ECE1; CCR5; BACE1; AVPR2; ACE;* | 13 |
| CC | Extracellular region | *VEGFA; TTR; PON1; NPPB; IGFBP3; GC; FGFR1; F7; F11; ERBB2; CTSD; CRP; APOB; ANXA1; ALB; ACHE;* | 16 |
| CC | Clathrin-coated endocytic vesicle membrane | *LDLR; APOB;* | 2 |
| CC | Cell surface | *VEGFA; VCAM1; PRLR; PLAU; HSPB1; HSPA8; CYP3A4; CCR5; ADRA1A; ADAM17;* | 10 |
| CC | Mitochondrion | *POR; PGR; NR3C1; NQO1; NFKBIA; NFKB1; MTOR; MT-CO3; MT-CO1; ITGB2; HSPA8; HSP90AA1; HK2; GSTP1; ESR2; CYP2D6; CYP27B1; CTSD; COX5B; COX5A; COX4I1; CASP3; BCL2; BAX; BID; BAD; APEX1; ANXA1; ADH1B; ABAT;* | 30 |
| CC | Exosomes | *TTR; SRC; SELP; RUVBL2; ROCK2; PTGS1; PRKCA; PPARG; PON1; PLAU; NQO1; MME; LCK; ITGB2; ICAM1; HSPB1; HSPA8; HSP90AA1; GSTP1; GRIN1; FABP1; F7; F11; ERBB2; EGFR; ECE1; DUOX2; CTSD; COX5B; COX4I1; CAV1; CASP9; BAX; ATP1A3; APOB; ANXA1; ALB; AKR1B1; AHSA1; ACP1; ACE; ABCC1;* | 42 |
| MF | Protein-tyrosine kinase activity | *SRC; LCK; JAK3; JAK2; JAK1; HCK; FYN;* | 7 |
| MF | Catalytic activity | *TYR; TNKS; PTGS1; POR; PARP1; MT-CO1; HSD11B1; HPSE; HMGCR; HK2; F11; DUOX2; CYP3A4; CYP2D6; CYP2C19; CYP27B1; CYP1A1; ADH1C; ADH1B;* | 19 |
| MF | Protein serine/threonine kinase activity | *ROCK2; ROCK1; RAF1; PRKCA; MYLK; MAPK8; MAPK10; IKBKB; GSK3B; DAPK1; CHEK2; CHEK1; BRAF; AKT2;* | 14 |
| MF | Ligand-dependent nuclear receptor activity | *PPARA; NR3C2; NR3C1; NR1I2; AR;* | 5 |
| MF | Kinase activity | *MTOR; CDK4; CDK2;* | 3 |
| MF | Extracellular ligand-gated ion channel activity | *GRIN2C; GRIN2B; GRIA2; CHRNA3;* | 4 |
| MF | Oxidoreductase activity | *NQO1; MT-CO3; CYP1B1; COX5B; COX5A; COX4I1; AKR1B1;* | 7 |
| MF | Aspartic-type signal peptidase activity | *CTSD; BACE1;* | 2 |
| MF | Transcription factor activity | *VDR; TP63; SREBF2; SREBF1; RUNX2; RELA; PPARG; NFKB1; NFE2L2; MYC; HSF1; HIF1A; FOS; ESR2; ESR1; ELK1; AHR;* | 17 |

Table S3: Pathway enrichment using the KEGG database

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| --- | --- | --- | --- |
| ID | Description | Gene identification | Count |
| hsa01522 | Endocrine resistance | *SRC/RB1/RAF1/MTOR/MAPK8/MAPK10/FOS/ESR2/ESR1/ERBB2/EGFR/CYP2D6/CDK4/CCND1/BRAF/BCL2/BAX/BAD/AKT2* | 19 |
| hsa01521 | EGFR tyrosine kinase inhibitor resistance | *VEGFA/SRC/RAF1/PRKCA/MTOR/JAK2/JAK1/IL6/GSK3B/ERBB2/EGFR/BRAF/BCL2/BAX/BAD/AKT2* | 16 |
| hsa04024 | cAMP signaling pathway | *ROCK2/ROCK1/RELA/RAF1/PTGER3/PPARA/OXTR/NFKBIA/NFKB1/MAPK8/MAPK10/GRIN2C/GRIN2B/GRIN1/GRIA2/FOS/CHRM2/CHRM1/CFTR/BRAF/BAD/ATP1A3/AKT2* | 23 |
| hsa04210 | Apoptosis | *RELA/RAF1/PARP1/NFKBIA/NFKB1/MAPK8/MAPK10/IKBKB/FOS/EIF2AK3/CTSD/CASP9/CASP3/BCL2/BAX/BID/BAD/AKT2* | 18 |
| hsa04012 | ErbB signaling pathway | *SRC/RAF1/PRKCA/MYC/MTOR/MAPK8/MAPK10/GSK3B/ERBB2/ELK1/EGFR/BRAF/BAD/AKT2* | 14 |
| hsa04151 | PI3K-Akt signaling pathway | *VEGFA/RELA/RAF1/PRLR/PRKCA/NFKB1/MYC/MTOR/JAK3/JAK2/JAK1/IL6/IKBKB/IGF2/HSP90AA1/GSK3B/FGFR1/ERBB2/EGFR/CHRM2/CHRM1/CDK4/CDK2/CCND1/CASP9/BCL2/BAD/AKT2* | 28 |
| hsa04510 | Focal adhesion | *VEGFA/SRC/ROCK2/ROCK1/RAF1/PRKCA/MYLK/MAPK8/MAPK10/GSK3B/FYN/ERBB2/ELK1/EGFR/CCND1/CAV1/BRAF/BCL2/BAD/AKT2* | 20 |
| hsa04071 | Sphingolipid signaling pathway | *ROCK2/ROCK1/RELA/RAF1/PRKCA/NFKB1/MAPK8/MAPK10/FYN/CTSD/BCL2/BAX/BID/AKT2/ABCC1* | 15 |
| hsa04115 | p53 signaling pathway | *IGFBP3/CHEK2/CHEK1/CDK4/CDK2/CCND1/CASP9/CASP3/BCL2/BAX/BID* | 11 |
| hsa01524 | Platinum drug resistance | *GSTP1/GSTM1/ERBB2/CASP9/CASP3/BCL2/BAX/BID/BAD/AKT2* | 10 |
| hsa04215 | Apoptosis – multiple species | *MAPK8/MAPK10/CASP9/CASP3/BCL2/BAX/BID* | 7 |
| hsa04062 | Chemokine signaling pathway | *SRC/ROCK2/ROCK1/RELA/RAF1/NFKBIA/NFKB1/JAK3/JAK2/IKBKB/HCK/GSK3B/CCR5/BRAF/BAD/AKT2* | 16 |
| hsa04066 | HIF-1 signaling pathway | *VEGFA/RELA/PRKCA/NFKB1/MTOR/IL6/HK2/HIF1A/ERBB2/EGFR/BCL2/AKT2* | 12 |
| hsa04080 | Neuroactive ligand-receptor interaction | *TBXA2R/PTGER3/PRLR/OXTR/NR3C1/HRH3/HRH2/GRM8/GRM5/GRM2/GRIN2C/GRIN2B/GRIN1/GRIA2/GCGR/DRD3/CNR1/CHRNA3/CHRM2/CHRM1/AVPR2/ADRA1A* | 22 |
| hsa04010 | MAPK signaling pathway | *VEGFA/RELA/RAF1/PRKCA/NFKB1/MYC/MAPK8/MAPK10/IKBKB/IGF2/HSPB1/HSPA8/FOS/FGFR1/ERBB2/ELK1/EGFR/CASP3/BRAF/AKT2* | 20 |
| hsa04218 | Cellular senescence | *RELA/RB1/RAF1/NFKB1/MYC/MTOR/IL6/IGFBP3/CHEK2/CHEK1/CDK4/CDK2/CCND1/AKT2* | 14 |
| hsa04380 | Osteoclast differentiation | *RELA/PPARG/NFKBIA/NFKB1/MAPK8/MAPK10/LCK/JAK1/IKBKB/FYN/FOS/AKT2* | 12 |
| hsa04370 | VEGF signaling pathway | *VEGFA/SRC/RAF1/PRKCA/HSPB1/CASP9/BAD/AKT2* | 8 |
| hsa00980 | Metabolism of xenobiotics by cytochrome P450 | *HSD11B1/GSTP1/GSTM1/CYP3A4/CYP2D6/CYP1B1/CYP1A1/ADH1C/ADH1B* | 9 |
| hsa04014 | Ras signaling pathway | *VEGFA/RELA/RAF1/PRKCA/NFKB1/MAPK8/MAPK10/IKBKB/IGF2/GRIN2B/GRIN1/FGFR1/ELK1/EGFR/BAD/AKT2* | 16 |